Update on perioperative evaluation and management of cardiac disease in vascular surgery patients

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Since the 1984 landmark publication by Hertzer and colleagues from the Cleveland Clinic, the co-existence of coronary artery disease (CAD) in patients with peripheral arterial disease (PAD) has been zealously embraced by the medical establishment.[1] In that widely quoted study, 1000 consecutive patients undergoing operations for PAD underwent preoperative cardiac catheterizations whether or not they had symptoms of CAD. The investigators reported that only 8% of their patients (roughly divided into thirds—aortic, infrainguinal, and carotid disease) had normal coronary arteries, whereas approximately one third had severe-correctable or severe-inoperable CAD. Complications of CAD (principally myocardial infarctions [MIs], congestive heart failure [CHF], unstable angina, and arrhythmias) remain the major causes of morbidity and mortality in this patient population.[2-5]

This study probably overestimates the prevalence of CAD in vascular patients, in part because epidemiologic studies have shown a decline in CAD in the general US population.[6-10] Approximately 25% of the reduction in the death rate occurring during the past 30 years is largely related to primary prevention and a better understanding of the events leading to coronary deaths.[11-13] These decreases in the incidence of new atherosclerotic disease will be offset by the aging of the so-called "baby boomer" population; it is estimated that one fifth of our population will be >65 years old by the year 2030.

The reportedly high prevalence of CAD in vascular patients has led to numerous evaluation and management algorithms. Little unanimity of opinion exists, and questions remain, including: (1) What events define coronary morbidity? (2) Which coronary artery lesions are most likely to produce adverse perioperative cardiac outcomes? (This question is of particular importance.) (3) Should the strategy for cardiac evaluation and management depend on the location of peripheral arterial atherosclerosis? (4) Is screening worthwhile, or should we assume that most vascular patients have CAD? (5) How "bad" are the adverse cardiac morbidity and mortality outcomes? (6) What is the safety and efficacy of the evaluation of and revascularization for CAD? (7) What is the role for perioperative "optimization" of patients suspected to have CAD? (8) With studies currently underway, what are our present recommendations?

This review summarizes the available data and speculates on current and future research.

DEFINING ADVERSE CARDIAC OUTCOMES-WHAT EVENTS DETERMINE CORONARY MORBIDITY?

Numerous adverse cardiac events have been evaluated and considered to be "end points" in clinical reviews of peripheral vascular operations, including: (1) unstable angina pectoris, (2) congestive heart failure (CHF), (3) arrhythmias, (4) myocardial ischemia (both overt and "silent"), and both (5) non-fatal MI and (6) fatal MI.[14] The first 4 are relatively "soft" outcomes. Although unstable angina is an acute coronary syndrome (ACS), it does not routinely produce lasting damage. Its definition is variable, ranging from a change in frequency of chest pain to unrelenting pain that is unresponsive to standard therapeutic maneuvers. CHF may result from fluid overload, often occurring after vascular procedures or after the use of a narcotic agent as a primary anesthetic.[15,16] Moreover, the criteria required to confirm a diagnosis are often subjective (jugular venous distention, dyspnea, rales, S_3, chest radiograph findings, pedal or sacral edema, objective measurement of decreased cardiac output—in variable combinations). Arrhythmias may be brief, self-limiting, hemodynamically benign, and caused by factors other than cardiac disease, including hypoxia, drug toxicity, or metabolic derangements. Myocardial ischemia occurs in 20% to 40% of patients; adverse events develop in >50% of patients.[17-19] The importance of perioperative myocardial ischemia detected by means of routine Holter monitoring has been shown,[20-25] although a recent report by Landesberg and associates indicated that during 11,132 patient-hours of monitoring after surgery, 38 of 185 consecutive patients had 66 transient ischemic events, but only 12 patients (6.5%) sustained perioperative MIs.[19] In addition, Kirwin and coworkers were unable to correlate silent myocardial ischemia on preoperative continuous ambulatory cardiogram (ECG; Holter) monitoring with perioperative MIs.[26]

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Competition of interest: nil.

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J Vasc Surg 2002;36:1292-308.

0741-5214/2002/$35.00 + 0 **24/1/129647**

doi:10.1067/mva.2002.129647

Nonfatal and fatal MIs are the most important and specific "hard" outcomes that determine cardiac morbidity. The diagnosis of acute MI, as defined by the World Health Organization (WHO) and recently revised by a Joint European Society of Cardiology/American College of Cardiology (ACC) committee, requires 2 of the these criteria: (1) a history of prolonged typical chest pain; (2) evolutionary changes on the ECG; (3) elevation of serial cardiac enzymes.[27,28] Symptoms are atypical or absent postoperatively in as many as 75% of patients who objectively exhibit MI, which is masked by residual anesthetic effects, analgesic agents, competing somatic stimuli such as incisional pain, etc.[29-35] ECGs are difficult to interpret and often do not exhibit classical ST-segment elevations or development of MI-associated Q waves.[36,37] (The principal method of statistical analyses of these sorts of committee definitions uses the BOGSAT technique—"Bunch of Guys Sitting Around a Table" [personal communication: Jerry Goldstone, Case Western Reserve University, Cleveland, Ohio].)

Traditional enzymes used as a means of determining MIs (creatine phosphokinase [CK]) may be released from skeletal muscle because of surgical trauma or ischemia/reperfusion injuries, which mask the isoenzyme CK-MB released from dying myocardial cells. Troponins (C, T, and I) are normal muscle proteins involved in the calcium-regulated, actin-myosin interactions.[38,39] Troponin I and T, but not C, exist as distinct cardiac-specific subtypes, and both qualitative and quantitative assays on the basis of antibodies to cardiac troponin T (cTnT) and I (cTnI) have been developed and approved by the US Food and Drug Administration (FDA) for use in the clinical diagnosis of MI. To date, most investigations have used cTnT as a means of determining the presence and extent of cardiac ischemia, but there is cross-reactivity with skeletal muscle troponin T.

In contrast, cTnI, found only in cardiac tissue, is 13 times more abundant in the myocardium than CK-MB. It is not detectable in the blood of healthy individuals or in patients with renal failure (as are CKMB and cTnT), and it may remain elevated for 7 to 10 days after an episode of myocardial necrosis.[40,41] CK and CK-MB are released only when this occurs. Elevation of cTnI has been shown to be an independent mortality risk factor in patients with unstable angina; non-Q-wave MIs and higher levels correlate with high mortality rates[42-46] and new regional wall motion abnormalities on echocardiography.[47] Each increase of 1 ng per milliliter in cTnI is associated with a significant increase ($P = .03$) in the risk ratio for death after adjustment for baseline characteristics.[48-50] Andrews and colleagues demonstrated that cTnI levels were accurate means of detecting myocardial ischemia in patients undergoing vascular surgery.[51] The currently accepted definition of MI (inapplicable to many earlier studies), recently formulated by the European Society of Cardiology/ACC in a consensus document, indicates its occurrence when cTnI levels are >3.1 ng/mL after prolonged ST-segment elevation.[52,53] Although much prose has been devoted to the importance of nTcI, ECG ST-segment changes are at least equally important in diagnosing cardiac injury after vascular operations.[54] Elliott M. Antman recently summarized decision-making with cardiac troponin tests in the *New England Journal of Medicine* (Jun 27, 2002).[55]

PATHOPHYSIOLOGY OF ACUTE CORONARY EVENTS-WHICH CORONARY LESIONS ARE MOST LIKELY TO PRODUCE ADVERSE OUTCOMES?

Primary MIs in patients who are ambulatory are most likely caused by stenoses <50% (ie, non-hemodynamically significant lesions), in contrast to PAD, in which higher-grade lesions are most likely to produce complications (eg, transient ischemic attacks, strokes, lower-extremity ischemia, etc).[56-74] Cardiac events result from disrupted atherosclerotic plaques, which need not be stenotic to rupture and cause occlusive thrombosis. The distribution of postoperative MIs is not necessarily the same as hemodynamically critical coronary artery lesions.[75] "Unstable" plaques have a large lipid core and a thin weakened fibrous cap infiltrated by macrophages and other inflammatory cells (Fig 1); these plaques are considered to be most vulnerable to disruption. Cytokines and proteases involved in the balance between synthesis and degradation of collagen and elastin that determine the structural integrity of the plaque cap play an important role.

There is great interest in the role of inflammation within or surrounding the plaque as a precursor of rupture. Unstable lesions may be especially prone to infection with chlamydia, cytomegalovirus, or helicobacter that may contribute to plaque instability or vulnerability. Evidence supporting the role of inflammation includes the visible presence of inflammatory cells in and around the lesion, activation of metalloproteinases near the plaque fissures, and finding a variety of inflammatory mediators in and around the lesion. Hence, C-reactive protein (a non-specific indicator of active inflammation) in the plasma is important as a long-term predictor of MI risk.[76-83] Aspirin's ability to reduce C-reactive protein levels and infarctions likely relates to both its antiplatelet and anti-inflammatory actions.[67,81,84] Inflammation within vulnerable coronary artery plaques may cause acute events by promoting rupture and erosion. Buffon and colleagues recently measured the neutrophil myeloperoxidase content in the cardiac and femoral circulations in patients with angina that was stable, recurrent, or unstable.[85] They reported widespread activation of neutrophils across the coronary vascular bed in patients with unstable angina, regardless of the location of the culprit stenosis, which challenges the concept of a single vulnerable plaque in acute coronary syndromes (Fig 2). There was significant correlation between systemic levels of C-reactive protein and neutrophil myeloperoxidase content in blood from the great cardiac vein. Thus, C-reactive protein levels and activated neutrophils are markers of widespread inflammatory processes. This possibility has important implications for research and therapy and challenges the widely accepted hypothesis that a

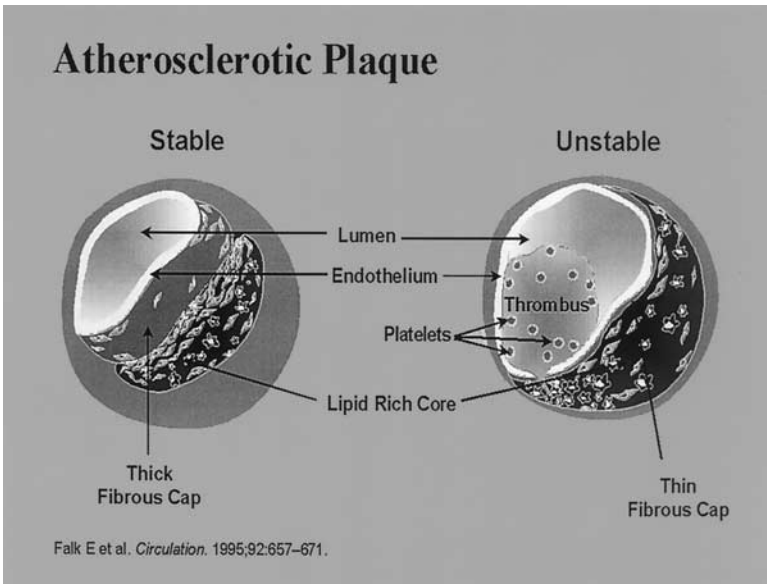

Fig 1. Line drawing of stable and unstable atherosclerotic plaques. Identification, intervention, or both for hemodynamically significant coronary artery lesions may not provide secure protection against perioperative adverse cardiac events after vascular surgery (see text for explanation). (Falk E, Fuster V. Angina pectoris and disease progression. Circulation 1995;92:2058-65. Copyright © 1995 Massachusetts Medical Society. All rights reserved.)

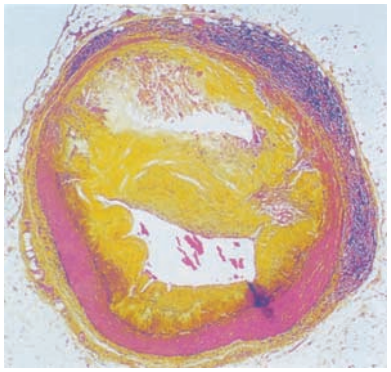

Fig 2. Color electron micrography shows extraordinary infiltration of myeloperoxidase-laden neutrophils into a section of coronary artery from a patient with unstable angina. Because this diffuse process is not localized to a single vulnerable plaque, focused therapy (eg, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) may not be protective against coronary events. Alternatively, anti-inflammatory (eg, antiplatelet therapy), stabilization with anti-lipid treatments, and β-blockers to decrease myocardial oxygen consumption may be more beneficial than mechanical approaches. (Buffon A, Fiasucci LM, Liusso G, et al. Widespread coronary inflammation in unstable angina. N Engl J Med 2002;347;5-12. Copyright © 2002 Massachusetts Medical Society. All rights reserved.)

single vulnerable plaque is responsible for the development of coronary instability, which questions the logic of percutaneous transluminal coronary angioplasty (PTCA)/stenting or bypass grafting for a presumed "index" plaque. Antiplatelet therapy may be even more effective in the big picture.[85-88]

Recognizing the unstable or vulnerable coronary artery plaque has led to "stabilizing" therapeutic approaches, such as administration of lipid-lowering medications (gemfibrozil, HMG Co-A reductase inhibitors ["statins"], niacin, etc), even in individuals with CAD but without demonstrable hyperlipidemias.[89-103] Sacks et al showed that disruption of coronary artery plaques can lead to neointimal proliferation, vasoconstriction, and occlusive thrombosis.[93,94,97,99,101,104] Pitt et al randomized 341 patients with stable CAD to receive treatment with atorvastatin versus revascularization.[104] The low-density lipoprotein level was maintained at <115 mg/dL of LDL versus percutaneous revascularization. This data showed that, in patients with stable CAD who are at low risk for myocardial infarction, aggressive lipid-lowering is at least as effective as angioplasty and usual care in reducing the incidence of ischemic events.[105] Because plaques do not need to be greatly stenotic to rupture and cause acute thrombosis, the Committee for the Mechanisms Precipitating Acute Cardiac Events has estimated that stenotic plaques are responsible for approximately one third of thrombotic events, although they may serve as a marker for the number of nonstenotic plaques present (ie, "atherosclerotic burden").[75] At present, there are no validated invasive or non-invasive methods for identifying plaques vulnerable to disruption in patients, which casts doubt on the relevance of current preoperative screening studies, because these tend to be a means of identifying hemody-

namically significant lesions that may or may not be unstable or vulnerable for producing acute coronary syndromes.

Identifying unstable or vulnerable plaque provides important pathophysiologic and therapeutic information for treating patients with CAD, whether or not they are undergoing non-cardiac operative procedures. Depré and colleagues in Belgium used directional coronary atherectomy and histologic and biochemical analysis of extracted plaque fragments to study coronary artery plaques. All plaque fragments retrieved from patients with stable angina were fibrous, whereas cellularity increased with unstable angina in proportion to the severity of the plaque instability score.[106] This corroborates the hypothesis put forth by Fuster and others that plaque thickness and stability is relatively "protective" against acute coronary events (as aforementioned).[71,107,108] Depré concluded that the morphologic pattern of coronary atherosclerotic lesions varies at different stages of acute coronary syndromes; different stages of angina correlate with an increasing prevalence of these morphologic characteristics: thrombus, atheroma, neovascularization, and cellular hyperplasia (ie, plaque thickness).

It is clear that a well-done provocative test that produces normal results confers a high negative-predictive value for perioperative cardiac problems. Virtually all available screening tests are means of assessing hemodynamic abnormalities in cardiac perfusion. If hemodynamically significant stenoses do not reliably produce cardiac events, "positive" test results have a low positive-predictive value. Prospective surveillance studies with screening ECGs and enzyme data report perioperative myocardial ischemia rates as high as 30% for ECG changes alone and 18% for those with cTnI elevations.[51] Landesberg et al reported a 32% incidence of perioperative myocardial ischemia after surgery.[18] In 1996, a *Journal of the American College of Cardiology* meta-analysis review article comparing intravenous dipyridamole-thallium-201 imaging and dobutamine echocardiography for risk stratification before surgery concluded that cardiac event rates were low in patients without a history of CAD (1% in 176 patients) compared with patients with CAD and a normal or fixed-deficit pattern (4.8% in 83 patients) or ≥1 thallium-201 redistribution abnormalities (18.6% in 97 patients, $P = .0001$).[109] Because of the diffuse nature of atherosclerosis, it is not surprising that CAD occurs with great frequency, regardless of the location of peripheral arterial occlusive disease. Most of the literature about cardiac morbidity has focused on patients requiring aortic reconstructions for either aneurysmal or occlusive disease. Myocardial damage in these patients was attributed to aortic crossclamping, declamping hypotension, and fluid shifts associated with major abdominal operations. However, investigators have consistently shown strikingly high occurrence of early and late cardiac morbidity in patients requiring infrainguinal arterial operations.

Hemodynamically positive test results may indicate a large coronary artery atherosclerotic "burden," thus warranting concern for postoperative cardiac complications. Thus, the index lesions identified with preoperative testing may not be a accurate means of predicting the precise myocardium at risk. The wide variety of available tests suggests that, thus far, no one study is a means of reliably predicting perioperative cardiac adverse consequences. Acute MIs may have been caused by plaque disruption at the site of hemodynamically insignificant coronary lesions.[110,111] Mickley showed that the demonstration of significant stenoses (>50%) often leads to mechanical revascularization, including PTCA or coronary artery bypass grafting (CABG), but coronary angiography is not an adequate means of predicting the location of the culprit plaque that will subsequently produce acute MI.[112] These studies apply to vascular surgery patients who are found to have relatively or completely asymptomatic CAD.

PREVALENCE OF ADVERSE CARDIAC EVENTS IN VASCULAR PATIENTS-SHOULD STRATEGY FOR CARDIAC EVALUATION AND MANAGEMENT DEPEND ON LOCATION OF PERIPHERAL ARTERIAL ATHEROSCLEROSIS?

The prevalence of CAD in PAD patients is widely accepted,[113-115] but the frequency of adverse cardiac outcomes is controversial. In the Cleveland Clinic study, hemodynamically significant CAD was demonstrated in 36% of patients with abdominal aortic aneurysms, 28% of patients with lower-extremity ischemia, and 32% of patients with extracranial carotid artery disease.[115] This prevalence is hard to dispute, but a comparison of morbidity rates between studies is often misleading because the frequency of cardiac complications depends on how vigorously the diagnosis is pursued.[116] On average, retrospective reviews (with clinical criteria like the Cleveland Clinic studies) report lower perioperative MI rates than series in which data are gathered in a proscribed prospective fashion. We have reviewed all major series reporting 100 or more patients, and the average MI rate after aortic, carotid, and infrainguinal operations; the published MI rates were 2.2% (7500 patients), 1.0% (28,000 patients), and 4% (6000 patients), respectively. According to our previously published studies, early adverse cardiac outcomes occur at least as frequently after infrainguinal procedures as aortic operations[117]; late events occur about twice as often in patients requiring infrainguinal operations as in patients undergoing aortic procedures (25% adverse cardiac events in patients requiring infrainguinal operations vs 8% in patients requiring aortic procedures at 2-year follow-up; $P = .04$).[118] L'Italien and coworkers reported a 2-fold acute increase in the early morbidity rate in infrainguinal procedures compared with aortic procedures (13% vs 6%).[119] Fewer postoperative events usually occur after carotid operations; the reported MI rate after carotid endarterectomy averages only 1.0% (see above).

In contrast, Ennix et al reported an operative mortality rate of 18.2% in 77 patients undergoing carotid endarterectomies without coronary revascularization, compared with a mortality rate of only 3% in 135 patients undergoing

either earlier coronary artery bypass grafting or simultaneous carotid endarterectomy and coronary artery bypass grafting.[1,120] Hertzer and Lees tracked 335 patients after carotid endarterectomies who were observed 6 to 11 years after surgery. MI caused 38.5% of the deaths that occurred within 11 years, accounting for 60% of early deaths within 30 days of surgery, which occurred in only 1.8% of the entire series. Although we have not performed a formal meta-analysis on this information, we estimate the average perioperative fatal/nonfatal MI rates associated with aortic, infrainguinal and carotid surgery to be 2.2%, 4.0%, and 1.2%, respectively. These estimates are far lower than what often appears in the literature. References for each series are available to readers by accessing our online sources. Our goal was to decipher true MI rates, a difficult feat for several reasons. For example, many studies report "adverse cardiac outcomes" rather than documented MI rates, whereas we discuss the problems of CHF and arrhythmias in "hard" outcome measures. In addition, although the literature may contain instances of "improved results," finding references to patients who experience extraordinarily high MI rates is less likely.

Review of the 41,500 patients having aortic, carotid, and infrainguinal operations discussed previously indicates several important trends: (1) the incidence of fatal/nonfatal MI after carotid surgery is by far the lowest of common vascular procedures; (2) the rate of MIs after aortic surgery averages about 2%, and the values remain fairly stable despite a plethora of strategies to avoid cardiac morbidity in the past decade; and (3) fatal/nonfatal MI rates after infrainguinal surgery (acutely) average approximately 4%, with a trend in decreasing rates in recent series, perhaps suggesting the strength of our data from the 1990s. Overall, improvements may also be related to the more widespread use of β-blockers or anesthesia optimization.

PREOPERATIVE SCREENING TESTS-IS IDENTIFICATION OF THE PATIENT AT HIGH RISK FOR CORONARY ARTERY DISEASE WORTHWHILE, OR IS IT PREFERABLE SIMPLY TO ASSUME THAT MOST VASCULAR PATIENTS HAVE SOME CORONARY ARTERY DISEASE?

As "outcomes research" comes of age, discussions of preoperative screening tests dominate the literature. A recent review article in the *New England Journal of Medicine* summarizes these tests in patients with stable CAD.[121] We have also summarized the strengths and weaknesses of many of these studies.[122,123]

The principal goals of preoperative identification of patients at high risk for adverse cardiac outcomes are to: (1) permit treatment of underlying CAD (eg, PTCA or CABG), (2) use more intensive or "safer" anesthetic techniques (eg, pulmonary artery pressure-monitoring catheters), (3) administer medications to decrease morbidity (eg, beta blockers), or (4) change preoperative plans (eg, performing axillobifemoral rather than direct aortic reconstruction for aortic occlusive disease). These tests range from completely noninvasive (eg, scoring systems), to minimally invasive (eg, echocardiographic estimation of ejection fraction), moderately invasive (eg, dipyridamole thallium screening tests), and very invasive (eg, coronary angiography), which underscores the absence of a consensus for optimal risk stratification. Various clinical risk indices have been proposed.[121,124-128,129-134] We and others recently reviewed the literature on screening.[123,135,136]

Additional recommendations for preoperative tests abound, as this abbreviated list describes: (1) exercise treadmill testing (ETT; eg, the "Bruce Protocol", which many vascular patients cannot undergo because of claudication, congestive heart disease, chronic lung disease, etc)[137-141]; (2) ambulatory electrocardiography (Holter monitoring)[14,24,25,117,142,143]; (3) radionuclide ventriculography (RNVG)[144-146]; (4) dipyridamole thallium scintigraphy (DTS)[32,147-156]; and (5) dobutamine or sestamibi stress echocardiography.[147,148,150,153] Numerous studies predicting the occurrence of adverse cardiac outcomes have also appeared (eg, a comparison of clinical examination, exercise testing, dobutamine stress echocardiography, and coronary arteriography by Therre et al).[157]

Most authorities agree that coronary angiography provides precise anatomic assessment of the status of CAD, but it is difficult to justify its routine use unless the patient's symptoms warrant revascularization on their own merits. Using decision analysis techniques, Mason and coworkers from Stanford University compared 3 strategies for dealing with CAD.[158] They found that vascular surgery without preoperative coronary angiography generally leads to better outcomes and that that procedure should be reserved for patients whose estimated mortality rate with surgery is substantially higher than average. Glance compared the cost-effectiveness of 4 preoperative screening strategies on the basis of mortality rates, morbidity rates, and cost data from a literature review,[159] concluding that selective screening before vascular surgery may improve 5-year survival rates and be cost-effective, especially when compared with routine angiography. The incremental cost-effectiveness ratio for selective screening was significantly lower than for routine angiography ($44,800/years of life saved [YLS] vs $93,300/YLS; $P < .02$). Other studies have described similar comparisons.[160]

As aforementioned, these tests rely heavily on the development of hemodynamically related symptoms (generally caused by hypoperfusion) or demonstration of a hemodynamically significant stenosis. Because we are unable to identify the most vulnerable and unstable plaques, these tests have failed as a means of reliably predicting postoperative myocardial events. Normal test results do correlate with absence of events, most likely because of a lesser atherosclerotic-CAD burden; this results in the good "negative-predictive value" of many studies, but the failure to predict adverse cardiac outcomes accurately. Poldermans' study of preoperative dobutamine stress echocardiography (DSE) in patients who subsequently died of acute MI and underwent autopsy by a pathologist unaware of the DSE results found a relatively poor correlation of the anatomic location of the infarction; in 50% of patients, the MI

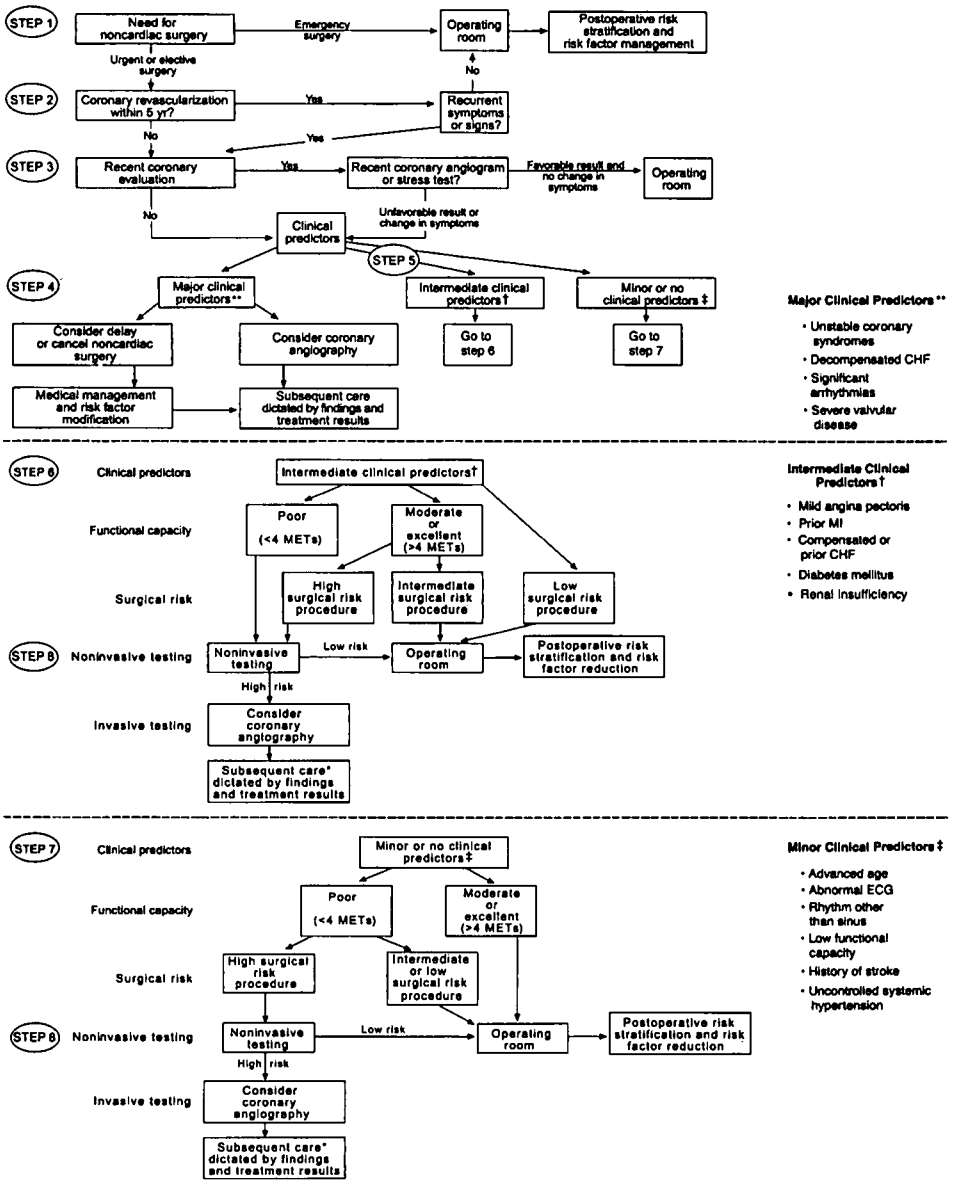

Fig 3. Algorithm recommended by the American College of Cardiology and American Heart Association. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA Guideline Update on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. American College of Cardiology/American Heart Association Practice Guidelines 2002;1-58.

extended beyond the ischemic territory assessed by means of DSE.[161] Poldermans concluded that perioperative medical therapy should be aimed at coronary plaque stabilization.

In 1996 and 2002, the ACC and the American Heart Association (AHA) appointed a task force to develop guidelines for perioperative cardiovascular evaluation for non-cardiac surgery. With the exception of Dr Norman Hertzer, a member of the 1996 committee, surgeons generally have been under-represented in this task force. The guidelines are an attempt to present "everything you ever wanted to know about cardiac disease in vascular patients;" however, the lack of surgical input and the complexity of the document limit its usefulness. Fig 3, online only is an algorithm that summarizes the ACC/AHA guidelines. Although there is much useful information in the publication, it is overwhelmingly complex.

Despite this, numerous publications have shown the usefulness of these guidelines. Samain et al retrospectively applied the guidelines to a group of 133 patients undergoing aortic surgery,[100] concluding that had the investigators used the guidelines, at least 1 cardiac-related death could

have been avoided. This is pure speculation. Farid and colleagues[162] at the Cleveland Clinic found abnormal test results in 27 of 181 patients scheduled for major surgery; 2 patients declined treatment, 8 patients had primary medical management, and 17 patients had cardiac catheterization with a variety of findings (including 2 "normal" results). Only 15% (27/180) of the patients with indications for a stress test had test results that were positive for cardiac disease; even fewer patients had any alteration of the perioperative period. On the basis of this study, the guidelines appear to have very little effect on perioperative outcome. We await the results of a recently completed prospective evaluation from the University of Michigan on implementing the ACC/AHA guidelines for preoperative cardiac risk assessment before aortic surgery (personal communication).

PERIOPERATIVE ADVERSE OUTCOMES—HOW "BAD" IS "BAD?"

Much of what is known about the incidence of acute MI and fatal coronary heart disease comes from isolated community surveillance studies,[113,163-165] cohort studies of cardiovascular disease,[166,167] or managed-care program studies.[168] We already discussed the apparent decrease in deaths caused by CAD in the general US population.[7,10,169]

In patients after surgery, adverse outcomes of transmural, Q-wave MIs are well documented. Mangano et al indicated that of 25 million patients who undergo noncardiac operations in the United States each year, approximately 3 million are at risk of having CAD; approximately 50,000 of these patients have a perioperative MI.[14] More than half of the 40,000 annual postoperative deaths are caused by transmural MIs.[5] In reviewing several thousand procedures, Hertzer found that cardiac complications were responsible for approximately half of all perioperative deaths; fatal events were nearly 5 times more likely to occur when standard preoperative indications of CAD were present.[114] Sprung and colleagues analyzed 6948 operations and found 107 patients with postoperative transmural MIs.[170] The 20.6% overall in-hospital mortality rate was highest on postoperative day 0. Similarly, Badner et al reported a 17% post-MI mortality rate after non-cardiac surgery.[171] Although these rates are better than those reported in older series (presumably because of improved anesthetic care, β-blockers, etc), a death rate from MI of almost 1 in 5 is startlingly high.

Furthermore, the late (5-year) mortality rate for vascular patients suspected of having CAD is twice that for patients not suspected of having it (approximately 40% vs 20%).[14] We reported an adverse cardiac outcome risk of 25% in patients who underwent infrainguinal bypass grafting in a short 2-year follow-up.[118] In Wilson's recent editorial, when René Leriché termed vascular intervention the "surgery of ruins," he attributed the shortened survival rate to systemic atherosclerosis.[172] Wilson went on to say, "As a rule of thumb, one can estimate a mortality rate of approximately 5% per year in patients who have undergone operation for arterial occlusive disease at any site." If anything, this estimate is probably low.

Some have questioned the clinical importance of non-Q-wave MIs (ie, "chemical" MIs) in vascular surgery patients. Yeager and colleagues observed 8 of 31 patients who sustained a perioperative MI with "chemical MIs" in which enzyme elevation was the sole indicator of postoperative MI.[173] At a mean follow-up period of 27.7 months, the survival rate for patients with nonfatal perioperative MI at 1 and 4 years was 80% and 51%, respectively, which did not differ significantly from that of control patients (90% and 60%, respectively; $P > .05$) Although, these investigators concluded, "a perioperative 'chemical MI' may not be a clinically significant clinical event, patients surviving nonfatal perioperative MIs after peripheral vascular surgery did have a higher incidence of subsequent adverse cardiac events and coronary artery revascularization." McFalls et al reported that, even in patients with perioperative transmural MIs, non-fatal perioperative MI was only a marginally significant independent predictor of the 1-year mortality rate ($P = .06$), whereas the extent of vascular disease at presentation was a more important determinant of long-term survival.[174]

Such optimism about the relative benign outcomes after "chemical" MIs is not supported by the literature. More than half of all acute MIs in the United States that occur in patients who are ambulatory are non-Q-wave MIs, and this proportion is rising.[164,170,175] Several investigations reported higher rates of both early and late ischemic complications, such as reinfarction and post-infarction angina, presumably because of the presence of viable but jeopardized myocardium within the perfusion zone of the artery responsible for the infarction.[175-186] The best management approach to non-Q-wave MIs is controversial. The 1987 ACC/AHA guidelines recommended routine coronary arteriography for all patients after non-Q-wave infarction[113]; newer guidelines no longer endorse this approach.[102,187] To determine the optimal treatment strategy for patients with non-Q-wave MIs, Boden et al performed a multicenter prospective randomized trial comparing invasive management (routine coronary angiography followed by myocardial revascularization) with conservative management (medical therapy and non-invasive testing).[175] The VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital) trial randomized 920 patients to 1 of the 2 strategies. A substantial 28% of cardiac events occurred during the follow-up period of 12 to 44 months, but the overall mortality rate did not differ significantly between groups. The investigators recommended a conservative, ischemia-guided initial approach. Although this study may be criticized for potential inapplicability to women, it cannot be said that patients cared for in Veterans Health Administration (VHA) hospitals received care of poorer quality than patients cared for elsewhere. Petersen et al compared 2486 veterans discharged from 81 VHA hospitals and 29,249 Medicare patients discharged from non-VHA hospitals and found no differ-

ence in mortality rates, even though VHA patients had more coexisting conditions.[146]

SAFETY AND EFFICACY OF EVALUATION AND REVASCULARIZATION FOR CORONARY ARTERY DISEASE-IS THERE A "DOWNSIDE" TO EXTENSIVE EXPLORATION/TREATMENT FOR CORONARY ARTERY DISEASE?

We recently performed a retrospective analysis of our experience with extended cardiac evaluations and interventions before vascular surgery at the Denver Veterans Administration Medical Center (VAMC).[188] These evaluations, which included standard screening studies and special tests such as echocardiography, radionuclide ventriculography, dipyridamole thallium scintigraphy, and cardiac catheterization, were performed in 42 patients. Nine patients (21%) underwent PTCA, and 7 patients (17%) underwent CABG. Unfavorable outcomes occurred in one third of patients who were subjected to an extensive preoperative assessment of risk in a 1-year period (Table I, online only). One fifth of the patients (8 patients) elected not to undergo the vascular procedures indicated. Most of these patients (7 of 8) had potentially life-threatening abdominal aortic aneurysms. Multiple reasons were cited for refusal, to the effect of "enough is enough." No difference in cardiac morbidity rates appeared between the patients who had extensive evaluations/interventions and the patients who did not (2.4% vs 2.9%; P = not significant). Patients refusing vascular surgery were of particular interest; in the recent ACC/AHA guidelines implementation review by Farid et al,[162] 3 of 27 patients (11%) who met ACC/AHA criteria either refused further treatment or never underwent the originally planned non-cardiac operations. Although these publications are relatively small, retrospective series and the VAMC study did not have a strict protocol for determining operative cardiac risk. We are concerned about the dearth of benefits from extensive CAD searches.

Controversy about what to do when severe, correctable CAD is identified also remains. Advocates of coronary revascularization before peripheral vascular operations contend that it both enhances the safety of the procedure itself and potentially prolongs life expectancy. We discussed the report by Ennix et al, in which prophylactic CABG markedly improved long-term survival rates after carotid endarterectomies.[120] Similar results were reported for patients who underwent PAD operations in other locations.[115,189-192] Many reports describe substantial numbers of patients who did very well after coronary revascularization, but they pertain to studies that were neither randomized nor prospective.

We urge caution in applying coronary revascularization before PAD surgery. Morbidity and mortality rates of CABG and PTCA in elderly patients with PAD are substantial. Cutler and Leppo examined 116 patients scheduled for operations with dipyridamole-thallium scintigraphy and referred 7 patients (6%) for CABG. One patient (14%) died after CABG; another died awaiting the procedure (14%).[193] No operative deaths occurred in the subsequent 106 operations; thus, the 2 deaths that occurred (1.7% of total) were directly related to the screening. A policy of prophylactic myocardial revascularization at the University of Iowa led to CABG procedures in 15 patients, with a mortality rate of 6.7% and postoperative complication rate of 20%.[194,195] Mesh and colleagues reported 3.6 times higher morbidity rates (39.7%) in patients with PAD who underwent CABG than patients without PAD (16.7%).[194] Often, the recovery from this major morbidity either precluded or substantially delayed the surgery for which the evaluation was undertaken. Even PTCA in patients with PAD carries higher morbidity and mortality rates than it does in patients without PAD.[196,197] The increased long-term survival rate in patients with CAD treated with coronary revascularization as proven by means of the CASS (Coronary Artery Surgery Study) trial may not apply to older patients with PAD, a strong, independent predictor of long-term mortality in patients with stable CAD. In addition, the CASS patients all had significant symptoms, whereas that may not be true for the patient with PAD whose CAD is discovered by means of provocative testing (ie, it may be unfair to extrapolate the CASS results to the PAD population).[198-200]

To date, there are no prospective randomized comparisons between "aggressive" cardiac management and best "conservative" medical care. Massie et al examined the results of coronary revascularization in patients versus control subjects,[201] observing ischemic responses to dipyridamole scans in 297 patients, of whom 70 underwent cardiac catheterization and 25 underwent coronary revascularization. No difference in adverse outcomes occurred between the coronary angiography group and 44% of the control group. Patients who underwent coronary angiography and were considered for cardiac revascularization had fewer cardiac events with a subsequent vascular operation than did the control subjects. However, any possible benefit from invasive cardiac evaluation was offset by 3 deaths and 2 MIs that complicated the cardiac evaluation. There was no significant difference in the rates of perioperative nonfatal MI (13% vs 0%), fatal MI (4% vs 3%), late non-fatal MI (16% vs 19%), or late cardiac death (10% vs 13%). In summary, the risks of extended cardiac evaluation and treatment did not produce any improvement in either the perioperative or long-term survival rate. The authors concluded that for most vascular surgery patients who have a positive results on a dipyridamole-thallium scan, coronary angiography does not provide additional useful information or benefit.

BEST MEDICAL CARE-WHAT ARE THE ROLES FOR PERIOPERATIVE "OPTIMIZATION" OF PATIENTS SUSPECTED TO HAVE CORONARY ARTERY DISEASE, INCLUDING THE USE OF B-BLOCKERS?

Optimizing a vascular patient's volume status by means of perioperative use of pulmonary artery catheters would seem to enhance the safety of surgery. Surprisingly, neither retrospective nor prospective trials have convincingly indicated this. Since 1980, reports have described attempts at

maintenance of optimal cardiac performance to improve results of vascular (particularly aortic) surgery. Whittemore and associates suggested that this was responsible for the low perioperative mortality rate and improved late survival rate in their patients, but the study was retrospective and based on historical control subjects.[202] More recent randomized, controlled trials of pulmonary artery catheters generally failed to improve outcomes. In 1997, Bender et al randomized 104 consecutive patients having major operations to a pulmonary artery catheter versus placement of a catheter "only if clinically indicated" (introducing potential bias into this study).[203] Except for a discrepancy in the amounts of fluids administered, there were no significant differences in outcomes or surgical intensive care unit length-of-stay, which suggested no benefit of routine pulmonary artery catheters in elective surgery patients. In 1998, Valentine and colleagues performed a truly randomized catheter trial.[204] One hundred twenty patients undergoing elective aortic surgery were randomized to placement of pulmonary artery catheters (n = 60) or the control group (intravenous hydration on the ward; n = 60). These investigators found no significant differences in the rates of cardiac morbidity, renal insufficiency, of pulmonary events or in the length of intensive care unit stay or length of hospital stay between groups, and they concluded that there was no benefit to routine catheter use. A recent meta-analysis of routine perioperative pulmonary artery catheterization indicated no effect on the rate of complications.[205]

Although in some of the aforementioned studies patients had pulmonary artery catheters placed while they were in the intensive care unit the day before surgery, the studies variably attempted to "optimize" the cardiac function of the patients involved. There is even more controversy with this. At least 10 studies have addressed perioperative homodynamic optimization to improve outcomes after vascular surgery, but most have been retrospective reviews with historical controls and contradictory findings.[202,206-211] Four prospective, randomized controlled trials of preoperative hemodynamic optimization of cardiac and volume status in vascular surgery patients showed no benefit, even when the goals of maintaining optimal arterial and venous oxygen saturations were achieved.[204,212-214] One "positive" randomized, prospective study of the effect of deliberate perioperative increase of oxygen delivery on mortality rates in high-risk patients with dopexamine hydrochloride showed improved outcomes, but this study was not limited to vascular surgery operations.[215] Thus, most randomized, prospective trials have failed to show significant benefits, and the costs to perform this routinely would be enormous.

There have been few reports on the efficacy of administering theoretically beneficial medications to prevent cardiac complications. For example, prophylactic nitroglycerin infusion during non-cardiac surgery does not reduce perioperative ischemia, as shown in a prospective, randomized study from Columbia University.[216] Another rather impractical study examined the efficacy of a small oral dose of clonidine in patients; although this drug was beneficial, the absorption of an oral agent is unpredictable in vascular surgery, and the work has not been confirmed by other studies 6 years later.[217] Finally, mivazerol, a drug with alpha2-agonist properties (the "active" counterpart of a β-Blocker) was evaluated in a randomized, blinded, prospective study of 1897 patients with CAD undergoing non-cardiac surgery (48% vascular surgery), with no alteration in the rates of MI or cardiac death.[218] Studies of this agent in vascular patients in the United States have been discontinued.

In contrast to the absence of efficacy of these drugs, it is now well accepted that β-blockade efficaciously reduces both short- and long-term cardiac morbidity and mortality rates. Selzman and colleagues recently wrote a review article of β-adrenergic blockade as prophylaxis against perioperative cardiovascular morbidity and mortality[219]; it reviews the history of β-adrenergic blockade and summarizes the pathophysiology of the mechanisms of action and data supporting its use in virtually all vascular patients. This is certainly not a new concept, although its popularity surged only after recent prospective trials proved the efficacy. Neurohormonal stress in surgery is at least in part related to adrenal cortical stimulation with catecholamine release, one of the links to perioperative myocardial ischemia associated with vascular and other serious operations.[220,221] Catecholamines increase each of the 4 major determinants of myocardial oxygen consumption (heart rate, preload, afterload, and contractility).[222] As early as 1982, Smulyan et al recommended continuous propranolol infusion after abdominal surgery.[223] Yeager and coworkers from OHSU reported reduction in perioperative MIs after vascular surgery with β-blockade.[134] This work and subsequent nonrandomized studies led to 5 controlled, randomized, prospective trials of perioperative blockade in patients (mostly vascular) with known or probable coexistent CAD. These studies are described in Table II, online only; all show a decrease in acute or chronic cardiac morbidity and mortality with β-blockade.[224-229] In summary, acute perioperative ischemic events, MIs, cardiac death, overall mortality, and adverse cardiac events generally decrease in frequency with the administration of β-blockers.[230] The advantageous effects relate to the decreased myocardial oxygen consumption they produce, as illustrated in Fig 4, which summarizes the methods by which myocardial oxygenation may be minimized.[222,230] Moreover, administration of β-blockers in the perioperative period is both safe and effective.[231]

CURRENT RECOMMENDATIONS-UNTIL PROSPECTIVE STUDIES CURRENTLY UNDERWAY ARE COMPLETED, WHAT ARE OUR RECOMMENDATIONS FOR OPTIMAL TREATMENT OF THE VASCULAR PATIENT WITH CORONARY ARTERY DISEASE?

This review is replete with disclaimers about retrospective studies, absence of control data, and a notable absence of level I data to guide treatment protocols.[105] Currently underway is a randomized prospective multicenter trial

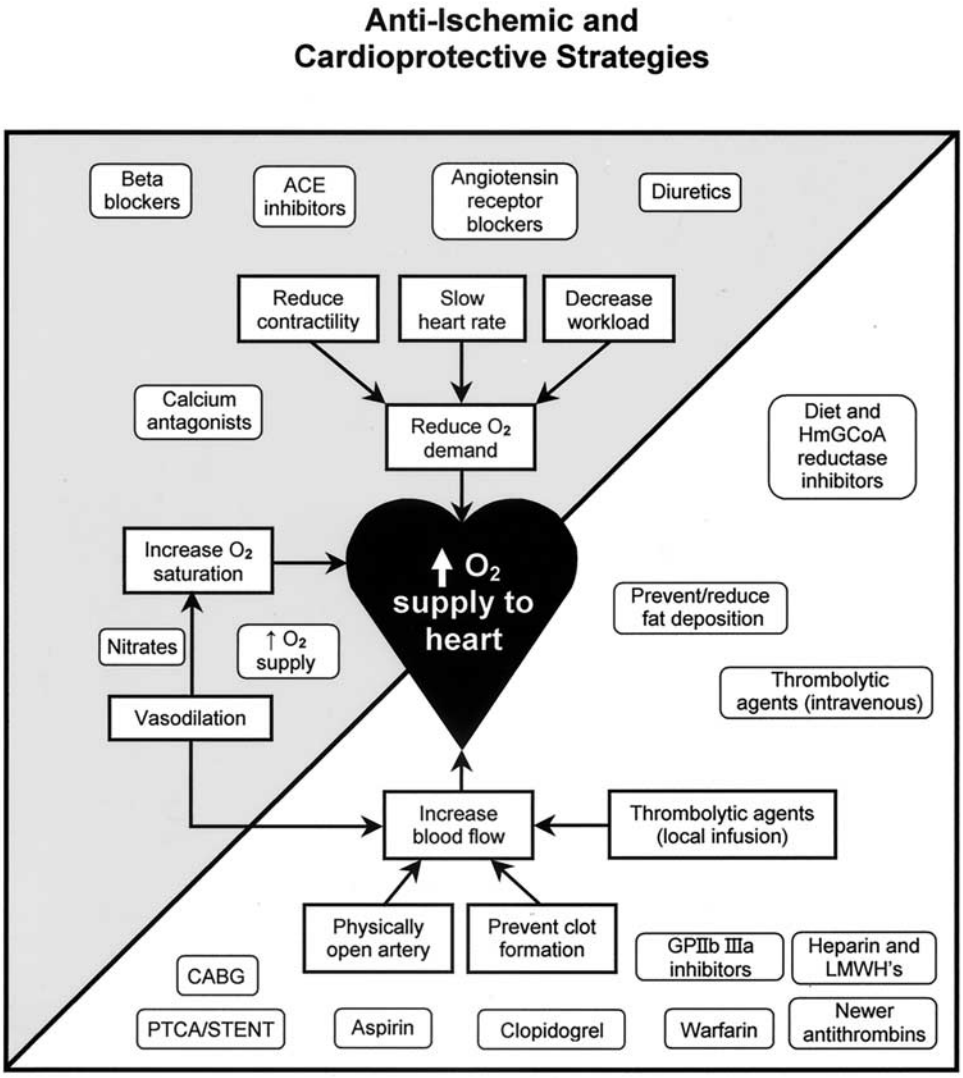

Fig 4. Factors that play a role in myocardial oxygen consumption.

that will provide extremely important information about optimal management. The protocol has been approved and funded by the Veterans Affairs (VA) Cooperative Studies Program (CSP) section; Mcfalls et al described a complete protocol.[174] Fig 5 summarizes the details of randomization and algorithm of the study, which is titled CARP (Coronary Artery Revascularization Prophylaxis). A sample size of 559 randomized patients will provide 90% power to detect a difference in 3.5-year survival rates of 75% versus 85%. By allowing for 10% of the patients to drop out after randomization, the final target sample size is 620 patients, which will be gathered at 18 high-quality VAMCs. As in every VA study, the results will suffer from a lack of women, and recruitment has been difficult thus far. Nevertheless, the study is proceeding remarkably well, and we are about halfway to completion. Only prospective randomization of comparable patients will provide the answer to whether coronary evaluation, revascularization, or both before elective vascular surgery enhances the safety of vascular surgery, prolongs the life of our patients, or both.

Until these results are available, we recommend keeping things simple. Rather than follow the ACC/AHA guidelines, we assume most of our vascular patients have at least some degree of CAD. Because β-blockade is clearly effective in decreasing cardiac morbidity, optimization of anesthesia and the use of β-blockers effectively decrease cardiac morbidity (as aforementioned). Fig 6 describes our current recommendations. Many "boxes" are identical (ie, operate, but assume most patients have some degree of CAD; use β-blockers in virtually all patients; and optimize the rate/pressure product in anesthesia). We avoid provocative tests, coronary revascularization, or both, except in unusual cases. When patients have severe CAD, consider-

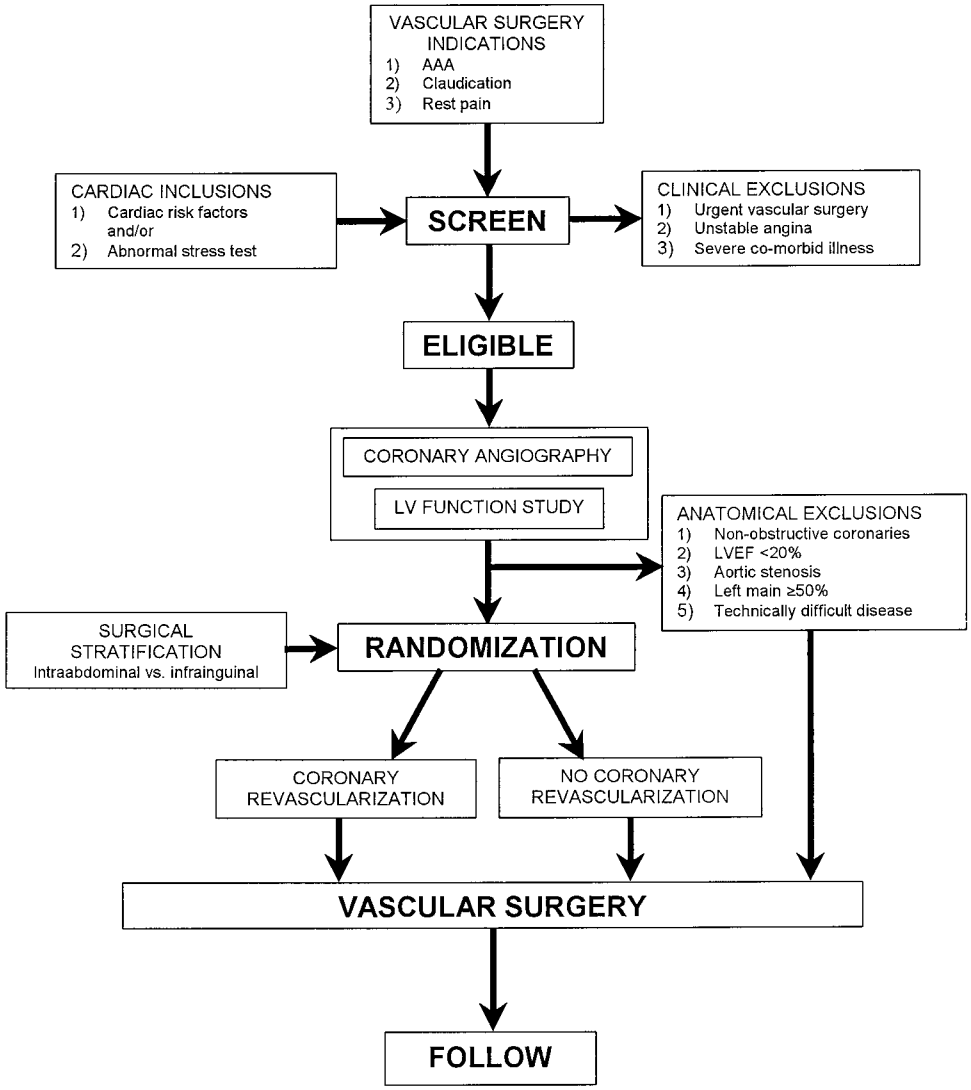

Fig 5. Algorithm of the CARP study (Coronary Artery Revascularization Prophylaxis), a Department of Veterans Affairs-sponsored study that is a randomized prospective multicenter trial to answer the hypothesis that coronary artery evaluation and revascularization will enhance the acute safety of peripheral arterial operations and increase long-term survival. *AAA,* Abdominal aortic aneurysm; *LVEF,* left ventricular ejection fraction; *LV,* left ventricular.

ation is given to modifying the planned operation or using conservative management.

Unfortunately, because CARP is a VA study with the disclaimers associated with most such investigations, it is likely that some controversy about optimal management strategies will persist. Fleisher and Eagle recently wrote a clinical practice guideline that concludes, "In high-risk patients scheduled to undergo non-cardiac surgery, coronary artery bypass grafting and percutaneous coronary revascularization are appropriate if they are indicated *independently* of the need for non-cardiac surgery."[232] We agree with this statement, as we do with K.E. Raby's editorial that concludes, "Is preoperative cardiac testing necessary among vascular patients? Based on the above body of evidence, the answer for most patients appears to be: No."[233] Bodenheimer has opined, "Otherwise, the tests should be skipped and the patient cleared [for vascular surgery]."[234] We also agree with the title of Itani, Miller, Guinn, and Jones' article: "Preoperative cardiac evaluation is unnecessary in most patients undergoing vascular operations."[235] Finally, we agree with Goldman's editorial in which he concludes, "The bad news is we still do not have all the answers. The good news is that approaches to the treatment of a cardiac patient undergoing non-cardiac surgery are increasingly being driven by data, including data from randomized clinical trials."[236]

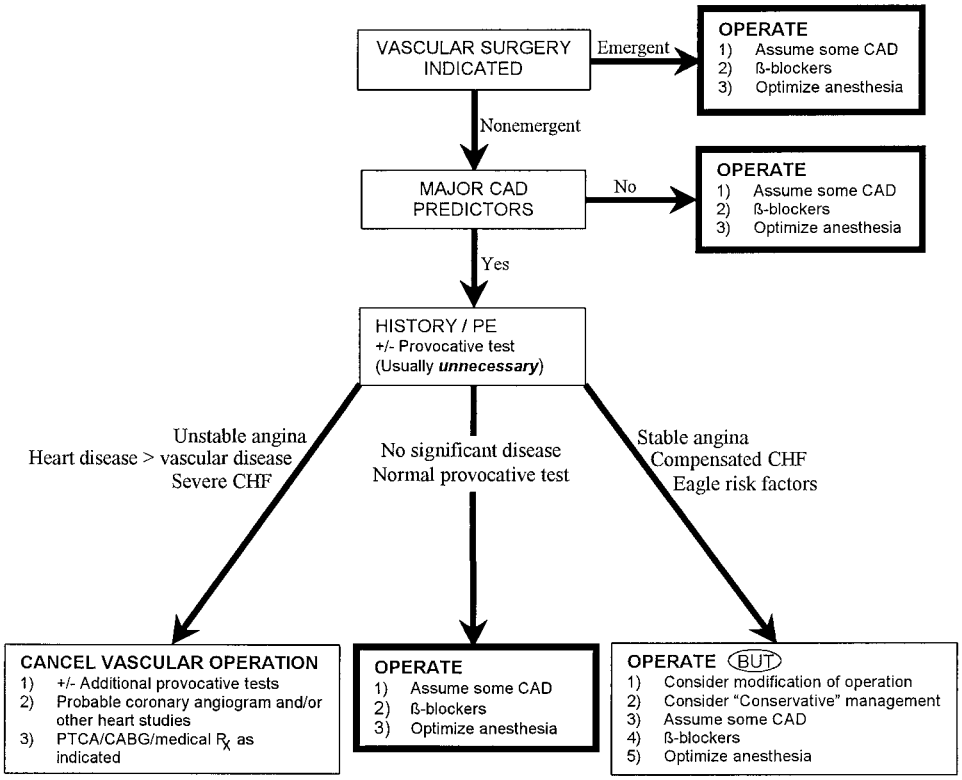

Fig 6. Our current recommendations for evaluation and treatment. Eagle risk factors include: (1) age >70; (2) myocardial infarction by history or Q-wave on electrocardiogram; (3) angina pectoris; (4) history of congestive heart failure (*CHF*); (5) diabetes mellitus; and (6) ventricular ectopy requiring therapy. *CABG,* Coronary artery bypass grafting; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *PE,* physical examination; *PTCA,* percutaneous transluminal coronary angioplasty/stent; R_x, therapy. Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Int Med 1989;119: 859-66.

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Submitted Jul 25, 2002; accepted Aug 26, 2002.

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Table I, online only. Adverse outcomes in 16 of 42 patients undergoing extended cardiac evaluations before major vascular surgery in a 1-year period at Denver Veterans Affairs Medical Center

Complication	*Number of patients*
Refused vascular surgery for which cardiac evaluation was undertaken	8
Limb loss caused by delay in vascular surgery during cardiac evaluation	2
Post-angiogram prosthetic graft infection requiring graft removal/revision	1
Femoral artery pseudoaneurysm requiring surgical repair	2
Sternal wound infection after CABG	1
Contrast-induced renal failure requiring hemodialysis	1
Anoxic brain injury after CABG	1
Total	16 (38%)

CABG, Coronary artery bypass grafting.
From Krupski WC, Nehler MR, Whitehill TA, et al. Negative impact of cardiac evaluation before vascular surgery. Vascular Medicine 2000;5:3-9.

Table II, online only. Controlled, randomized trials of perioperative β-blockade (references and details listed in text)

					Results	
Source	*Year*	*N*	*Drug*	*Follow-up*	*Control*	*β-blockers*
Stone	1988	128	Control = 39 Labetalol = 29 Atenolol = 30 Oxprenolol = 30	Intraoperative	28% ischemia	2% ischemia $P < .001$
Mangano	1996	200	Control = 101 Atenolol = 99	2 years	21% mortality	10% mortality $P < .019$
Poldermans	1999	112	Control = 53 Bisoprolol = 59	30 days	17% cardiac death	3.4% cardiac death $P = .02$
Raby	1999	26	Control = 11 Esmolol = 15	48 hours	73% persistent ischemia	33% persistent ischemia $P < .05$
Urban	2000	107	Control = 55 Esmolol = 52	48 hours	15% ischemia 6% MI 16% cardiac morbidity	6% ischemia 2% MI 11% cardiac morbidity P = NS
Poldermans	2001	101	Control = 44 Bisoprolol = 57	2 years	32% cardiac events	12% cardiac events $P = .025$

MI, Myocardial infarction; *NS*, not significant.